Reversal of Mechanical Hyperalgesia by a Dual-Acting, Peripherally Restricted kappa/delta Opioid Agonist (CAV1001) in a Rat Model of Inflammatory Arthritis

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Background

Rheumatoid arthritis (RA) is a chronic inflammatory pain condition. In RA and other inflammatory states, normally sequestered peripheral delta opioid receptors may become active, allowing delta-opioid agonists to participate in the pain pathway directly and through allosteric modulation of peripheral kappa opioid receptors.1

Purpose

This study evaluated the efficacy of a single intraperitoneal injection of CAV1001 (a novel dual-acting, peripherally restricted kappa/delta opioid agonist) on hyperalgesic nociceptive behaviors in the CFA (Complete Freund’s Adjuvant) Model of Inflammatory Arthritis Pain in Rats.

Methods

- Following IACUC approval, inflammatory arthritis pain was induced with injection of 50 μL CFA into the tibio-tarsal joint;
- Mechanical hyperalgesia was assessed via joint compression thresholds (JCTs);
- 50 animals were randomly assigned to 5 groups (Power: 80%);
- Ipsilateral and contralateral joint compression thresholds (JCTs) were assessed prior to CFA injection, predosing on Day 0, and 1, 2, and 4 hours post-dosing;
- Animals were administered a single dose of vehicle, CAV1001 (1, 5, or 10 mg/kg IP), or celecoxib (30 mg/kg PO: active control; internal validity) on day 0 (14 days after CFA);
- All behavioral evaluations were performed by a blinded observer;
- Mechanical hyperalgesia was measured using a digital Randall-Selitto device.

Study Design: Arthritis (CFA Ankle)

<table>
<thead>
<tr>
<th>Post Surgery</th>
<th>Serum Creatinine</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Ileitis (Control)</td>
<td>N/A</td>
<td>10</td>
</tr>
<tr>
<td>2 CAV1001</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>3 CAV1001</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>4 CAV1001</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>5 Celecoxib</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Results

Arthritis: Hyperalgesia Development

Unpaired t-test, two-tailed, ipsilateral vs. contralateral.

Result

<table>
<thead>
<tr>
<th>Time Point</th>
<th>t</th>
<th>DF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Injection Baseline</td>
<td>1.22</td>
<td>18</td>
<td>0.240</td>
</tr>
<tr>
<td>Pre-Dosing Baseline</td>
<td>4.13</td>
<td>18</td>
<td>0.0007</td>
</tr>
<tr>
<td>1 Hour</td>
<td>4.66</td>
<td>18</td>
<td>0.0002</td>
</tr>
<tr>
<td>2 Hour</td>
<td>5.56</td>
<td>18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>4 Hour</td>
<td>5.56</td>
<td>18</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

+++: p<0.001 (t test);
**: p<0.01 (one-way ANOVA);
***: p<0.001 (one-way ANOVA)

Arthritis: Results

- CAV1001 (10 mg/kg) significantly increased paw compression thresholds compared to vehicle at all time points, (p<0.001, one-way ANOVA);
- CAV1001 (1 mg/kg and 5 mg/kg) significantly improved paw compression thresholds at both the 2-hour and 4-hour time points (p<0.01, one-way ANOVA);
- Celecoxib did not significantly improve thresholds at 1-hour but did at the 2-hour and 4-hour time points (p<0.001, t test).

Arthritis: Model Development

- CAV1001 (10 mg/kg) significantly increased paw compression thresholds compared to vehicle at all time points, (p<0.001, one-way ANOVA);
- CAV1001 (1 mg/kg and 5 mg/kg) significantly improved paw compression thresholds at both the 2-hour and 4-hour time points (p<0.01, one-way ANOVA);
- Celecoxib did not significantly improve thresholds at 1-hour but did at the 2-hour and 4-hour time points (p<0.001, t test).

Conclusion

Intraperitoneal administration of CAV1001 significantly reversed CFA-induced mechanical hyperalgesia. The reversal in mechanical hyperalgesia with CAV1001 1 mg/kg was comparable to the active control, celecoxib.

Reference


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